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EXAMINER	
BRISTOL, LYNN ANNE	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,417	KRIEG, PAUL A.	
	Examiner	**Art Unit**	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _05 October 2009_.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _1-13,15,16,18-26 and 28-30_ is/are pending in the application.

4a) Of the above claim(s) _15,16 and 18-20_ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1-13, 21-26 and 28-30_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/5/09 has been entered.

2. Claims 1-13, 15, 16, 18-26, 28-30 are all the pending claims for this application.

3. Claims 15, 16 and 18-20 are withdrawn from examination.

4. Claims 1-13, 21-26 and 28-30 are all the pending claims under examination.

5. This Office Action contains new grounds for rejection.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

6. The rejection of Claims 1-13, 21-26, and 28-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained.

In the Office Action of 4/19/07, the grounds for rejection were based on the breadth of claim scope for any apelin inhibitor having any anti-angiogenic (or anti-tumorigenic [now deleted]) effect under any conditions in any subject including a human. The rejection was maintained as set forth in the Office Action of 12/7/07 as follows:

"A) The specification and prior art is not enabling for apelin antisense therapy

In the Office Action of 4/19/07, the Examiner acknowledged the working examples in the specification for inhibiting vascular growth or angiogenesis in a frog embryo with antisense DNA for apelin (Example 5), apelin expression being increased in approximately one third of 154 human tumor samples compared to non-tumor tissue based on dot-blot hybridization analysis with labeled cDNA probe for human apelin (Example 6) and upregulation of apelin under hypoxic conditions in primary rat cardiomyocte cells strongly suggestive for apelin's role in tumor angiogenesis (Example 7). Applicants' specification demonstrates functional activity for one single embodiment, an apelin antisense molecule decreasing vascular permeability in a CAM assay.

Applicants allege on p. 14, ¶2 of the Response of 9/19/07 "the specification does in fact disclose a model suggesting that an apelin inhibitor could be administered to a human patient in order to inhibit angiogenesis or tumorigenesis. Example 5 shows that an apelin antisense oligonucleotide inhibits angiogenesis in the angiogenesis model system of Xenopus embryos." Further, the Declaration of Dr. Kreig (sec. 6) asserts "an apelin antisense oligonucleotide does in fact inhibit angiogenesis" in an art-accepted model.

With respect to the use of antisense molecules, at the time the instant invention was filed, the art recognized significant unpredictability to equate phenotypes derived from antisense technology with phenotypes derived from true loss-of-function methods. According to **Stein (Pharmacology and Therapeutics 85: 231-236, 2000)**:

> "[A]ntisense oligonucleotide biotechnology has entered a phase of its development in which many problems engendered by non-sequence specificity are being recognized and being actively addressed. However, in order to improve specificity of the methodology, attention must now also be aid to co-suppression of gene activity due to irrelevant cleavage." Stein further states that "[T]o the extent that this issue also is addressed, correlations between the down-regulation of a defined target and an observed biological outcome (e.g., growth suppression) *eventually* [*emphasis added*] may be possible." (page 235, Concluding remarks)

Stein clearly suggests that use of antisense oligonucleotide therapeutics are highly unpredictable due to "irrelevant cleavage" as a result of the low stringency requirements for RNAse H activity, wherein a 5-base complementary region of oligomer to target may be sufficient to elicit RNAse H activity (see Stein, abstract).

Stein also teaches (**J. Clinical Investigation 108(5): 641-644, 2001**) that:

> "serious question have arisen as to whether an observed biological effect in an antisense experiment has indeed been produce by an antisense mechanism, or whether it is due to a complex combination of non-sequence specific effects. Investigators must therefore understand how to employ antisense technology properly and should recognize its limitations" (page 641, column 1, paragraph 2). However, in many, and perhaps most of the citations in which only a single oligomer was evaluated, the results reported may represent some combination of true antisense effects with sequence-nonspecific and cytotoxic effects" (page 642, column 1, lines 20-25). Except under rare and strongly justified circumstances, the use of an observed biological endpoint to claim antisense efficacy is not acceptable (page 642, column 2, lines 6-10).

Stein teaches several guidelines that reflect the state of the art at the time of filing of the instant application, including: (a) that although computer-based approaches are being developed, it is still necessary to choose the optimal antisense oligonucleotide sequence from a panel of oligonucleotides, e.g. by mRNA "walking", (b) down-regulation of a relevant molecular target must be demonstrated, and (c) maximizing sequence specificity and minimize sequence non-specificity.

Stein teaches that only approximately one in eight (12.5%) of the putative antisense oligonucleotides tested can be shown to be active (page 642, column 1, lines 14-18). Other useful controls include:

> (i) the use of two or more oligonucleotides of different sequences that are complementary to the same target. If the observed phenotype(s) are the same or distinct from those seen using control oligonucleotides, an antisense mechanism of target downregulation is strengthened, (ii) introduction of the target gene with one or more mutations in the region complementary to the antisense oligonucleotide. Lack of antisense inhibition in this case is

suggestive, particularly if the antisense oligomer is still effective when the wildtype target is forcibly over-expressed (page 642, column 1, lines 40-65).

Caplen (**Gene Therapy 11(16): 1241-1248, 2004**) addresses the degree of unpredictability in the art when choosing a biologically effective antisense sequence, stating that "it is unclear at this time (2004) what the minimum level of homology required between the siRNA and the target to decrease gene expression is, but it has been reported that matches of as few as 11 consecutive nucleotides can affect the RNA levels of a non-targeted transcript" (page 1245, column 2). This is especially relevant in mammalian cells because mammalian cells have nonspecific dsRNA-triggered responses primarily mediated through interferon-associated pathways that are absent in invertebrates and plants. While RNAi appears to be easy to induce, critical analysis of RNAi derived phenotypic data should not be overlooked. The validation of the RNAi effect in mammalian cells is important and that non-specific effects of RNAi need to be carefully assessed in mammalian cells (page 1245). For example, "ensuring the specificity and quantifying the efficacy of the particular siRNA or shRNA against a clinically relevant target transcript is essential in justifying its further development."

With regard to the ability of an artisan to correlate an observed antisense RNA phenotype to a predicted phenotype using targeting vectors that knock-out, gene disruption by selective ablation is the most definitive approach. Caplen teaches that the RNAi machinery can be saturated, so there will probably be a limit to the number of different genes that can be targeted in a cell at one time (page 1244, column 1). Furthermore, Caplen expresses the importance in recognizing that there is variation in the degree of inhibition mediated by different small interfering RNA sequences which may result in the production of different phenotypes. Thus, the disclosure of a phenotype in response to the expression of a single, structurally undefined antisense molecule (page 24, Example 4, Table 2, discussed below) cannot reasonably predict the phenotype obtained when the individual gene is totally disrupted.

Delivery

In regards to the delivery of oligonucleotide pharmaceutical compositions *in vivo*, the state of the art indicates that delivery of these oligonucleotide compositions for therapeutic purposes "remains an important and inordinately difficult challenge (**Chirila et al, Biomaterials 23:321-342, 2002**, see abstract)." At the time of filing of the instant application there were no general guidelines for successful *in vivo* delivery of antisense compounds known in the art. Problems related to the pharmaceutical use of nucleic acids in general, and antisense and siRNA nucleic acids in particular, are evident from the pre- and post-filing art. One problem is the inability to routinely deliver an effective concentration of a specific nucleic acid into a target cell, such that a target gene or miRNA is inhibited to a degree necessary to produce a therapeutic effect--in this case inhibition of RNA silencing of a gene.

Gerwirtz et al. (Blood 92(3): 712-736, 1998) for example, teach that "...delivery of oligonucleotides remains an important problem..." (page 728). "The ability to deliver ODN into cells and have them reach their target in a bioavailable form must be further investigated. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient." (page 728)

Jen et al. (Stem Cells 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. "One of the major limitations for the therapeutic use of AS-ODNS [anti-sense oligonucleotides] and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." (page 313, second column, second paragraph) It is also concluded that "[a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (See page 315, last two paragraphs).

Chirila et al. (Biomaterials 23:321-342, 2002, page 327, last paragraph) teach that "[T]he *in vivo* delivery techniques chiefly used at the present, i.e. infusion or injection of naked molecules and liposomal systems, do not assure adequately long-term maintenance of ODNS [oligonucleotides] in tissues," which is required to achieve therapeutic effects. As a conclusion to the review of Chirila et al, the state of oligonucleotide based drug therapy is summarized by the statement: "the antisense strategy only awaits a suitable delivery system in order to live up to its promise."

Opalinska et al. (Nature Reviews 1:503-514, 2002) teach that: "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA". "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded." (page 511, columns 1-2)

Scherer et al (Nature Biotechnology 21(12), pages 1457-1465, 2003) teach that antisense oligonucleotides (ODNs), ribozymes, DNAzymes and RNA interference (RNAi) each face remarkably similar problems for effective application: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the

target RNAs. Scherer et al teach that these challenges have been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can become widely accepted as a therapeutic agent.

Kurreck et al (Current Opinion Drug Discovery and Development 7(2): 179-187, 2004) teaches that "many potential sites are inaccessible for complementary oligonucleotides due to the secondary and tertiary structures of the long RNA molecule. Furthermore, RNA-binding proteins shield some regions of the mRNA" (page 179).

Lu et al (RNA Interference Technology, Cambridge, Appasani, ed., 2005, page 303) state that "Unlike *in vitro* transfection of siRNA into cells, *in vivo* delivery of siRNA into targeted tissue in animal models is much more complicated, involving physical, chemical and biological approaches, and in some cases their combination." Therapeutic applications, however, clearly depend upon optimized local and systemic delivery of siRNA *in vivo*. "....limited reports of *in vivo* studies have indicated a lack of effective delivery methods for siRNA agents." "...the two most critical hurdles are maintaining its [siRNA] stability *in vivo* and delivery to disease tissues and cells." (page 314) Lu et al. admit that while hydrodynamic delivery of siRNA duplexes into mouse liver has proven to be quite efficient, this technique is not clinically feasible in human studies.

Samarsky et al (RNA Interference Technology, Cambridge, Appasani, ed., 2005, pages 389-394) appear to agree with Lu et al., stating that "Delivery of RNAi to target cells and tissues in mammalian organism[s] is considerably more difficult than in cultured cells. This step is likely to be a critical bottleneck in the *in vivo* application of RNAi." "One major remaining obstacle is the efficient delivery of RNAi triggers to target tissues *in vivo*." (page 394)

Sioud (RNA Silencing, Methods and Protocols, Humana Press, 2005) expresses similar reservations, specifically with respect to the use of cationic carriers, as currently claimed in claims 34 and 35. On page 238, Sioud states "Despite some encouraging results, however, liposomes still have not the characteristics to be perfect carriers because of toxicity, short circulation time, and limited intracellular delivery for target cells." And on page 243, "The *in vivo* uptake of siRNAs can differ dramatically with cell types as well as with the status of cell differentiation." "...certain synthetic siRNAs activated the production of TNF-alpha and interleukin (IL)-6 in human freshly isolated monocytes...

Similarly, **Simeoni et al (RNA Silencing, Methods and Protocols, Humana Press, 2005, page 251**) state "So far, although siRNA transfection can be achieved with classical laboratory-cultured cell lines using lipid-based formulations, siRNA delivery remains a major challenge for many cell lines and there is still no reasonably efficient method for *in vivo* application."

Mahato et al. (Expert Opinion on Drug Delivery, January 2005, Vol. 2, No.1, pages 3-28) teach that antisense oligodeoxynucleotides and double-stranded small interfering RNAs have great potential for the treatment of many severe and debilitating diseases. Mahato et al. teach that efforts have made significant progress in turning these nucleic acid drugs into therapeutics, and there is already one FDA-approved antisense drug in the clinic. Mahato et al. teach that despite the success of one product and several other ongoing clinical trials, challenges still exist in their stability, cellular uptake, disposition, site-specific delivery and therapeutic efficacy. Mahato et al. teach that in order for siRNAs to be used as therapeutic molecules several problems have to be overcome, including: the selection of the best sequence-specific siRNA for the gene to be targeted and the ability to minimize degradation in the body fluids and tissues.

The efficacy of antisense-based therapies hinges upon the ability to deliver a sufficient amount of oligonucleotide, to the appropriate tissues, and for a sufficient period of time, to produce the desired therapeutic effect. So far, it appears that all of the developments in antisense-based therapies have not been sufficient to overcome this one basic obstacle, drug delivery. The art teaches that the behavior of oligonucleotide-based compositions and their delivery *in vivo* are unpredictable, therefore claims to pharmaceutical compositions and methods of treating diseases by the administration of oligonucleotide-based pharmaceuticals are subject to the question of enablement due to the high level of unpredictability associated with this technique as taught in the prior art.

In view of the express teachings of the art suggesting that *in vivo* delivery of siRNA is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the pharmaceutical compositions of the instant invention to target any desired gene in any cell in any animal to effect the desired outcome. The skilled artisan would not know a *priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in any tissue in any organism such as any mammal, including humans, in a sufficient concentration and remaining for a sufficient time to activate target-specific RNA interference of any desired gene. Specific guidance would be required to teach one of skill in the art how to deliver single-stranded small interfering RNA molecules to cells *in vivo* to produce a measurable effect in an organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Cell culture examples are generally not predictive of *in vivo* inhibition, and the methods of delivery to a cultured cell, e.g., *D. melanogaster* embryos and worms, is not expected to be routinely applicable to the delivery of oligonucleotides to all other organisms, including mammals. The state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

At the time of filing of the instant application, no general guidelines for successful *in vivo* delivery of antisense compounds known in the art, nor are such guidelines provided in the specification as filed. The specification provides general, not specific, guidelines regarding i) an amount of single-stranded small interfering RNA "sufficient for degradation of the target mRNA to occur, thereby activating target-specific RNAi in the organism", ii) physical methods of introducing nucleic acids into an organism, and iii) pharmaceutical compositions formulated to be compatible with its intended route of administration.

A review of the instant application fails to find adequate representations or guidance exemplifying the *in vivo* applications currently contemplated for which the pharmaceutical compositions are intended. There are no working examples wherein Applicants have successfully delivered the inventive ss-iRNA nucleic acid molecule(s) to an animal *in vivo*, wherein an angiogensis-associated diseased state was successfully treated, and wherein the treatment effects were directly correlated with the administration of the inventive ss-RNA nucleic acid molecule(s) to said animal *in vivo*. Instead, the single working example is directed to a method for reducing angiogenesis in a CAM assay.

No technical guidance or exemplary disclosure is provided regarding the use of the claimed methods for targeting genes in living organisms, including any mammal, which is the subject of the invention. As the art indicates, *in culture* results are not readily extrapolated to *in vivo* applications. Furthermore, Applicant contemplates that the method of treating a disease or disorder may include the application or administration of a therapeutic agent to an isolated biological sample from a patient. However, the specification fails to disclose how the administration of a single-stranded RNA molecule *ex vivo* to a sample derived from a patient suffering from a disease will effect the treatment of a disease *in the organism* [emphasis added], e.g., a disease process that is cell-autonomous, such as an inborn error of metabolism, that will ameliorate the symptoms of the organism suffering from said cell-autonomous disease.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed methods in the manner disclosed to produce the intended effects of activating target-specific RNA interference to treat angiogenesis or a disease or disorder associated with the activity of apelin protein. Furthermore, Applicant's specification does not provide actual working examples or guidance so that the skilled artisan can deliver the pharmaceutical compositions of the claimed invention to target tissues successfully, to produce the desired therapeutic result without undue experimentation.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Therefore, the specification does not describe the use of single-stranded siRNA molecules for the *in vivo* treatment of a disease or condition associated with the expression of a target protein, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present inventive methods without undue experimentation. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treatment leading to the amelioration of conditions associated with the expression of a target protein in a patient) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention. For example, the instant application does not appear to teach one of skill in the art how to effectively target tissues and cells in any mammalian sample in vitro or in vivo. Similarly, while the instant application is enabling for the use of single-stranded siRNA *in ova* (e.g., birds), it does not enable the use of these RNAs *in vivo* in other multicellular organisms, such as mammals, including humans.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention(s) commensurate with the claimed scope. In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method(s) commensurate with the scope of the claimed invention(s). Accordingly, the instant claims for apelin antisense molecules are rejected for failing to comply with the enablement requirement.

B) The specification and prior art is not enabling for inhibiting angiogenesis with any apelin antibody in any subject much less a human

In the Office Action of 4/19/07, the Examiner acknowledged the specification teaching "Other apelin antagonists are antibodies and fragments thereof" at [0027]. The specification does not demonstrate any working models for an inhibitory apelin antibody more especially one that interferes with apelin peptide/receptor interaction or apelin peptide/APJ interaction. The specification does not provide enablement for inhibiting angiogenesis with any antibody recognizing apelin peptides of SEQ ID NOs:1-5, or treating a biological sample in a human having any angiogenesis- associated disorder with any apelin inhibitor much less any one apelin antibody recognizing peptides of SEQ ID NOs:1-5.

Applicants' allege that "antibodies were known at the time of filing that specifically bind apelin (citing Kleinz et al., Regul. Peptides 118:119-125 (2004))" (p. 15 of the Response of 9/19/07). The Declaration of Kreig (sec. 9) alleges that "others have identified additional antibodies that specifically bind apelin."

Applicants have not provided a copy of the Kleinz reference to verify the assertion that the antibodies of Kleinz could inhibit apelin activity, block apelin peptide receptor interactions or block apelin interaction with APJ much less whether any of the Kleinz antibodies were shown to inhibit angiogenesis in a relevant mammalian model.

Applicants' response is incomplete.

Applicants' allege that the Declaration of Kreig demonstrates an apelin antibody that specifically inhibits angiogenesis in the CAM assay (p. 15 of the Response of 9/19/07). The Declaration of Kreig alleges that four anti-apelin antibodies were produced (ab206, ab207, ab208 and ab210), that two antibodies significantly reduced endothelial cell proliferation in vitro (ab208 and ab210; Exhibit A) and the ab208 Ab inhibited angiogenesis in the CAM assay (Exhibit B).

The Examiner respectfully submits that Applicants have not disclosed which of the apelin epitopes the antibodies were made to, thus one of skill could not reasonably conclude that the ab206, ab207, ab208 and ab210 could bind to any

one or more of peptides of SEQ ID NO: 1-5. Further, the specification and declaration evidence does not demonstrate that apelin antibodies that do bind peptides of SEQ ID NOs:1-5 can generate anti-angiogenesis responses in any sample from any subject, in any species and to what degree. Applicants have not shown whether any apelin antibodies were effective at blocking angiogenesis in a relevant mammalian model, again instead relying on *in ova* data from birds. Applicants have not shown biodistribution data, or with dose response data what if any effective levels of antibody therapy could be achieved in vivo for any given disorder associated with angiogenesis in a mammalian in vivo model.

Applicants have not addressed the cited references of record as they apply to administering any antibody immunotherapy in vivo.

C) The specification and prior art is not enabling for inhibiting apelin activity in a human with an antibody against zebrafish apelin (SEQ ID NO:5)

In the Office Action of 4/19/07, the Examiner questioned the relevancy of an anti apelin antibody binding to a peptide of SEQ ID NO:5 from zebrafish apelin, more especially in practicing the instant claimed methods of treating angiogenesis in a human.

Applicants did not address this aspect of the rejection. The Declaration of Dr. Kreig does not address this aspect of the rejection.

Applicants' response is incomplete."

The rejection was maintained as set forth in the Office Action of 9/5/08 as follows:

"Applicants' allegations on pp.2-4 of the Response of 6/10/08 have been considered but are not found persuasive. Applicants' response to each of sections A-C above, are addressed below.

A. Applicants allege that because one (1) out of the twelve (12) references relied on by the Examiner in showing the overall art-recognized unpredictability of anti-sense therapy, instead makes the *mere* suggestion that "the antisense strategy only awaits a suitable delivery system in order to live up to its promise", effectively negates the other teachings. Applicants maintain the predictability for anti-sense treatment still further in view of Example 5 in the specification, which shows anti-apelin antisense molecule can block angiogenesis in an in vitro frog embryo assay.

Response to Arguments

Applicants' claims are directed to methods of inhibiting angiogenesis in a biological sample which encompasses any sample in vitro much less in vivo and where the subject may be a human. Further, the method encompasses a therapeutic for treating an angiogenesis-related cancer in a human subject. The examiner acknowledges the frog embryo model within its own context but is hard pressed to enter Applicants attorney-based arguments that a single in vitro model could be extrapolated to any in vivo animal model much less a human clinical trial.

The complexity of extrapolating any drug discovery from "bench to bedside" is underscored by numerous reports in the literature. Translation of therapeutics from in vitro to in vivo use is unpredictable. A tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and drug access to the tumor cells are not evenly distributed and this is an important source of heterogeneity in tumor response to drugs. Therefore, prediction of drug effects in any animal model much less a human based solely on a single in vitro frog embryo model experiment as in the present case is not reliable and further evaluation in animal angiogenic tumor systems is essential.

Further, inasmuch as in vitro drug testing may be a platform technology in a determination of enablement, the complexity and difficulty of drug delivery for cancer treatment is underscored by Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos

suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar.

Cespdes et al. (Clin. Transl. Oncol. 8(5):318-329 (2006)) review the some of the examples of art-recognized animal disease model correlates for the corresponding human disease in Tables 1-3. Cespedes emphasizes the challenges in using animal models as predictive correlates for human responsiveness to therapeutics and sets forth on pp. 318-319 a list of criteria that would represent the ideal in vivo model for studying cancer therapeutics. As regards the use of xenograft modeling, Cespedes teaches:

> "One limitation of the xenograft models is precisely their use of an immunocompromised host, which eliminates the possibility of studying the role of the immune system in tumor progression. Some authors also think that cancer and host cells being from different species may limit the occurrence of critical tumor-stroma interactions, leading to an inefficient signaling. The organ of implantation could also become a limitation to the system. Thus, as it has already been described, subcutaneous xenografts infrequently metastasize and are unable to predict response to drugs" (p. 325, Col. 1, ¶2).

One skilled in the art would reasonably conclude that evidence obtained from the in vitro frog embryo modes would not even necessarily correlate with results expected in a relevant angiogenic tumor animal model much less in humans.

B. Applicants allege the Kleinz reference (Kleinz et al. Regul. Peptides 118:119-125 (2004); Exhibit A) demonstrates examples of two apelin antibodies binding to two apelin peptides and "one of skill in the art will recognize that binding of the anti-apelin antibodies to apelin peptides can inhibit apelin activity, block apelin peptide receptor interactions or block apelin interaction with APJ"; and Applicants are not required to demonstrate which of the antibodies, ab206, ab 207, ab 208, and ab 210, bind to the peptides of SEQ ID NOS: 1-5 or that the antibodies can generate anti-angiogenesis responses in any sample from any subject in any species and to what degree.

Response to Arguments

First, and because the claims are directed to antibodies having the ability to bind to one or more of the peptide species as set forth in the Markush group, Applicants are required to show the cross-reactivity for the antibodies amongst the different peptides. The claim language requires that the antibody bind any one or any more than one of the combination of peptides, and Applicants have yet to demonstrate cross-reactivity for any antibody reduced to practice much less that the cross-reactive antibody would have an apelin inhibitory effect on tumor angiogenesis in a relevant model.

Second, Applicants are not exonerated from having to meet the burden for enablement especially for antibody immunotherapeutics, where as in the present case, a limited number of experiments do not provide the sufficient correlation or nexus for the use of the antibody to treat a cancer in vivo much less in a human. Here, a relevant model would be an animal model at least bearing some resemblance to tumor angiogenesis. See the references of record from the Office Action of 4/19/07 discussing the unpredictability of antibody immunotherapeutics in tumor treatment. These references taken together with the references cited above under section A, along with the limited number of working examples in the specification and the Declaration evidence of 9/19/07 are dispositive to the full scope of the claims being enabled. The examiner has established and has properly maintained the rejection of the claims based on the preponderance of the evidence (MPEP 706).

C. Applicants allege that SEQ ID NO:5, which is a peptide from zebra fish and differs by only one amino acid from the human-derived apelin peptide of SEQ ID NO:4, should generate similar antibodies relative to the antibodies of SEQ ID NO:4.

Response to Arguments

Applicants have not shown that the zebra fish peptide is relevant to any tumor angiogenesis model, that the peptide would generate a therapeutic antibody and that the same antibody would possess tumor angiogenesis-

inhibitory activity in vivo. Absent a showing to the contrary, arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection (MPEP 2144.03).

Applicants allegations on pp. 6-10 of the Response of 10/5/09 have been considered and are not found persuasive. Applicants summarize the Examiner's arguments on pp. 6-7.

a) On pp. 7-8 of the Response, Applicants allege "The specification provides sufficient working examples showing that an inhibitor of apelin activity, e.g., an apelin antisense DNA, does inhibit vascular growth or angiogenesis in an art-accepted animal model (e.g., Example 5). The Declaration of Dr. Krieg, dated September I8, 2007, also demonstrates that "an apelin antisense oligonucleotide does in fact inhibit angiogenesis" in an art-accepted model. Although the art recognized unpredictability in the use of antisense molecules, Applicants respectfully submit that given this demonstration, it would be reasonably expected that other antisense apelin inhibitors could routinely be made and tested and, therefore, enabled such that one skilled in the art could practice the claimed invention."

Response to Arguments

The claims encompass any anti-angiogenic factor including anti-sense RNA for apelin mRNA where the explicit effect is to inhibit angiogenesis and the implied intended effect is to produce an anti-cancer effect (see for example, Claim 5 which is drawn to further administering an anti-cancer agent). The examiner submits and re-iterates that absent detailed and careful experimentation, the ordinary artisan could not predict the effect of just any anti-apelin anti-sense RNA having an anti-angiogenic effect much less an anti-cancer effect.

At the time of filing of the instant application, no general guidelines for successful *in vivo* delivery of antisense compounds known in the art, nor are such guidelines provided in the specification as filed. The specification provides general, not specific, guidelines regarding i) an amount of single-stranded small interfering RNA “sufficient for degradation of the target mRNA to occur, thereby activating target-specific RNAi in the organism”, ii) physical methods of introducing nucleic acids into an organism, and iii) pharmaceutical compositions formulated to be compatible with its intended route of administration.

A review of the instant application fails to find adequate representations or guidance exemplifying the *in vivo* applications currently contemplated for which the pharmaceutical compositions are intended. There are no working examples wherein Applicants have successfully delivered the inventive ss-iRNA nucleic acid molecule(s) to an animal *in vivo*, wherein an angiogensis-associated diseased state was successfully treated, and wherein the treatment effects were directly correlated with the administration of the inventive ss-RNA nucleic acid molecule(s) to said animal *in vivo*.

Applicants are requested to access the Cabic website (www.Cabic.com) and to consider the presentation by J. Douglas Schultz from the June 2007 USPTO Biotechnology Customer Partnership Meeting providing guidance for claiming RNAi methods (entitled “Patenting Interfering RNA”). Applicants have yet to claim a single known apelin RNAi by its sequence identifier in order to enable the ordinary artisan to practice the full scope of the method invention.

b) On pp. 8-9 of the Response, Applicants allege "With respect to the Office Action's requirement to show the cross-reactivity for the antibodies amongst the different peptides to demonstrate that the antibodies could bind to any one or more of the peptides of SEQ ID NO: 1-5, Applicants respectfully submit that one skilled in the art would appreciate that the generation of antibodies is routine in the art as are methods of determining the specificity, effectiveness, and cross-reactivity of those antibodies. Determining those additional antibodies bind to and inhibit the activity of apelin as expected is routine. In fact, the specification, together with the relevant skill in the art, enables one to practice the claimed invention, because the generation and screening of antibodies to one or more peptides is routine in the art."

Response to Arguments

The claims encompass any anti-angiogenic factor including inhibitory antibodies for apelin where the explicit effect is to inhibit angiogenesis and the implied intended effect is to produce an anti-cancer effect (see for example Claim 5 which is drawn to further administering an anti-cancer agent). The examiner submits and re-iterates that absent detailed and careful experimentation, the ordinary artisan could not predict the effect of just any anti-apelin antibody having an anti-angiogenic effect much less an anti-cancer effect. The prior art supports this position and is dispositive to Applicants attorney arguments that it is easy to make an antibody against apelin peptides and that would both a) bind apelin in vitro and in vivo and b) be functionalized to mediate a therapeutic effect.

Four (4) art references spanning nearly 20 years in the field of immuno-therapeutics and as recognizing the complexity of antibody delivery to tumors in vivo are Fujimori et al. (J. Nuc. Med. 31:1191-1198 (1990)); Beckman et al. (Can. 109:170-179 (2007)); Thurber et al. (Adv. Drug Deliv. Rev. 60:1421-1434 (2008)); and Rudnick et al. (Can. Biotherp. & Radiopharm. 24: 155-162 (2009)).

Fujimori teaches for further understanding of Mab distribution in the tumor, one must consider as well the microscopic pharmacology: transport across the capillary wall, transport in tumor interstitium, cellular binding and metabolism. Fujimori discusses predictive models for accessing tumor antigen availability by Mab to examine the relationship between affinity and distribution. Fujimori teaches on p. 1196, Col. 2, ¶1:

> "One strategy to overcome the binding-site barrier would be to increase the initial Mab dose. Even though Mab concentration in tumor does not always increase linearly as initial Mab concentration increases, a high initial plasma concentration leads to better percolation and results in more uniform distribution in tumor. Increasing Mab dose, however, decreases the specificity ratio and may cause toxicity or other side effects. For each Mab species and set of circumstances, there is an inherent balance of factors. Other causes of heterogeneous distribution include the functional and anatomical heterogeneity of tumors and their vessels..., and the elevated interstitial tissues..."

Beckman teaches on p. 175, Col. 2, ¶2-4:

> "Optimizing biodistribution properties of Ab constructs depends on a large number of host and tumor variables. These include: the density and distribution of target Ag in tumors and normal tissues: the degree of target occupancy and residence tiemr equired for tumor cell kill; possible toxicities from normal tissue distribution; tumor size and vascularity; tumor interstitial pressure, convection and diffusion; and metabolism and internilzation rates for Ab-Ag constructs.

An equally large number of Ab construct and therapy variables are available for optimization, including size, charge, and valence; constant region type and glycosylation pattern; presence or absence of a radioisotope or a toxic moiety; dose, route, and schedule of administration; and use of a traditional or a pretargeting strategy. Given the complexity of the problem, systematic preclinical programs may enhance the likelihood of success in subsequent clinical studies. Such preclinical investigations should integrate both experimental and theoretical approaches.

Preclinical studies of a putative Ab-based therapeutic agent can encompass a variety of constructs, differing in molecular weight, affinity, valence, and/or other features of interest, which bind to the same epitope as demonstrated by competition experiments. The Ag density and target affinities should be known for both tumor cells and cross-reacting normal tissues, and the percent target occupancy and required residence time for tumor cell kill should ideally be investigated in vitro. Similarly, rate constants for Ab-Ag internalization should be determined, if applicable. Dose and schedule should be varied and antitumor efficacy, pharmacokinetics, overall biodistribution, homogeneity of intratumoral distribution, and tumor microvessel density and distribution ideally should be measured in tumor-bearing animals with a variety of tumor sizes."

Studies in tumor-bearing rodents are often confounded by lack of normal tissue reactivity with Ab constructs directed toward human Ags, but studies in transgenic animal can be performed in some instances to alleviate this issue."

Thurber teaches on p. 1431, Col 2, ¶3:

"Analyzing the fundamental rates that determine antibody uptake and distribution provides a theoretical framework for understanding and interpreting targeting experiments and improving on

the limitations of uptake. It also provides a background for a more rational design of in vitro experiments, animal studies, and clinical trials. The insight gained from this type of modeling has multiple implications for imaging and therapy. For example, not all cells are exposed to the "average" concentration obtained in a tumor. A significant portion of cells can survive even if the tumor-averaged concentration is well above the LD50 in vitro. Also, the concentration that cells in a solid tumor are exposed to ([Ab]surf) is well below the plasma concentration. This means that the bulk antibody concentration in an in vitro spheroid experiment is not analogous to the plasma concentration but is actually well below it; large doses are required to overcome this poor extravasation. Knowing the rate of uptake in a tumor and clearance from the plasma and normal tissues also provides estimates of ratios between tumor and normal tissue concentrations, and these ratios are important in both imaging and therapy. These examples illustrate the utility of combining theoretical analysis also suggest ways to rationally improve uptake, and determining the limiting rates is the first step in overcoming these problems."

Rudnick teaches on p. 155, Col. 2:

"Not strictly limited to tumor cells, target antigen is commonly expressed on normal tissue, found in circulation, and shed into the tumor interstitial space. These nontarget pools of antigens can reduce treatment effectiveness, increase systemic clearance, and increase side-effects (especially for radioimmunoconjugates) by impairing mAb specificity for the tumor."

and on p. 158, Col. 2, last ¶ - p. 159, Col. 1:

"...antigen selection will be a critical factor for internalization and catabolism of mAbs. The relative rates of antigen recycling and dissociation are important in mAb penetration into tumors. Therefore, in applications dependent on targeting every cell of a tumor, the mAb needs to dissociate before it is internalized and degraded. In the case of ADCC, a slow internalizing antigen would be the best target. However, if one is trying to deliver a cytotoxic agent to the cytoplasm of cells in a limited region of a tumor, such as the vasculature, a mAb with slow dissociation targeting a rapidly recycling antigen would be appropriate. These are just simple examples of the interplay of affinity, avidity, and efficacy in tumor targeting."

Finally and absent a showing to the contrary, arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection and more especially in the instant case where counsel of record asserts common knowledge about the state of the art for antibodies without substantiating evidence (MPEP 2144.03).

c) On p. 9 of the Response, Applicants allege “similar to SEQ ID NO:4, the specification clearly states that SEQ ID NO:5 is one of the "apelin polypeptides" that refer to a polypeptide that comprises the C-terminal 13 amino acids of apelin ("apelin-13"). As previously discussed, SEQ ID NO:5 and SEQ ID NO:4 differs by only one amino acid. Since Example 3 of the specification provides an example demonstrating the angiogenic effect of SEQ ID NO:4, the specification does not need to provide the angiogenic effect for all apelin-13 peptides, including SEQ ID NO:5.

Response to Arguments

It has been well known that minor structural differences even among structurally related compounds can result in substantially different binding activities for the same antibody. For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document).

Thus it not predictable that an antibody that binds the peptide of SEQ ID NO:4

would also bind the peptide of SEQ ID NO:5 having the single amino acid change much less that the same antibody would also have the properties of inhibiting apelin activity, inhibiting angiogenesis, decreasing vascular permeability, interferes with the interaction of an apelin polypeptide or apelin peptide with a receptor polypeptide, and interferes with the interaction of an apelin polypeptide or apelin peptide with APJ.

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

7. Claims 1-13, 21-26 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-13, 21-26 and 28-30 are interpreted as being drawn to the genus for a composition comprising any apelin inhibitor under the sun known and yet to be discovered and which has the properties of 1) inhibiting angiogenesis (an impliedly inhibiting cancer); 2) decreasing vascular permeability, 3) interfering with the interaction

of an apelin polypeptide or apelin peptide with a receptor polypeptide, and 4) interfering with the interaction of an apelin polypeptide or apelin peptide with APJ.

The specification and the prior art do not nearly support the genus of apelin inhibitors to place Applicants in possession of the genus at the time of filing. Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials 3/25/08), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: The specification discloses compositions comprising apelin antagonists which competitively bind to a downstream or upstream member of the cell membrane component metabolic cascade that includes the apelin polypeptide [0044], and for compositions inhibiting apelin activity indirectly, such as a specific endopeptidase and “belonging to the subtilisin family of serine proteases (Barr, 1991, Cell 66:1-3)” [0045] which putatively cleave apelin to the 13 amino acid and 17 amino acid peptides. Other apelin antagonists are antibodies and fragments thereof [0027].

Example 5 discloses inhibiting vascular growth or angiogenesis in a frog embryo with antisense DNA for apelin using primers of SEQ ID NOS: 6 and 7.

Example 6 of the specification teaches apelin expression was increased in approximately one third of 154 human tumor samples compared to non-tumor tissue based on dot-blot hybridization analysis with labeled cDNA probe for human apelin.

Example 7 discloses that upregulation of apelin under hypoxic conditions in primary rat cardiomyocte cells strongly suggest that apelin plays a role in tumor angiogenesis.

The specification does not support the scope of apelin inhibitors for the instant claimed invention much less demonstrate an actual reduction to practice for the genus of species.

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the genus of apelin inhibitors having the properties of 1) inhibiting angiogenesis (an impliedly inhibiting cancer); 2) decreasing vascular permeability, 3) interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor polypeptide, and 4) interfering with the interaction of an apelin polypeptide or apelin peptide with APJ.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of apelin inhibitors having the properties of 1) inhibiting angiogenesis (an impliedly inhibiting cancer); 2) decreasing vascular permeability, 3) interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor polypeptide, and 4) interfering with the interaction of an apelin polypeptide or apelin peptide with APJ.

d) Method of making the claimed invention: the specification teaches inhibiting vascular growth or angiogenesis in a frog embryo with antisense DNA for apelin using primers of SEQ ID NOS: 6 and 7.

e) Level of skill and knowledge in the art: the level of skill for identification of apelin inhibitors having the properties of 1) inhibiting angiogenesis (an impliedly inhibiting cancer); 2) decreasing vascular permeability, 3) interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor polypeptide, and 4) interfering with the interaction of an apelin polypeptide or apelin peptide with APJ exceeds the written description in the specification for the screening assays and myriad possible inhibitors falling into biological or pharmaceutical chemical arts.

f) Predictability in the Art: the art does not appear to teach the genus of apelin inhibitors at the time of filing and having the properties of 1) inhibiting angiogenesis (an impliedly inhibiting cancer); 2) decreasing vascular permeability, 3) interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor polypeptide, and 4) interfering with the interaction of an apelin polypeptide or apelin peptide with APJ.

Applicants have not demonstrated with sufficient evidence the genus of apelin inhibitors comprising any structure and having all of the following properties 1) inhibiting angiogenesis (an impliedly inhibiting cancer); 2) decreasing vascular permeability, 3) interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor polypeptide, and 4) interfering with the interaction of an apelin polypeptide or apelin peptide with APJ.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-13, 21-26 and 28-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 and 19 of copending Application No. 11/333830 (US 20060159676). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '803 are drawn to a species of angiogenesis disorder (lymphangiogenesis) that reads on and overlaps with the instant claims for a method of inhibiting the genus of angiogenesis (MPEP 2131.02).

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The claims of '830 are as follows:

1. A method of inhibiting lymphangiogenesis in a biological sample, comprising: a. providing a biological sample; and b. combining the sample with a lymphangiogenesis-inhibiting amount of a composition comprising an inhibitor of apelin activity.

2. The method of claim 1, wherein the composition interferes with the interaction of an apelin polypeptide or apelin peptide with a receptor polypeptide.

3. The method of claim 1, wherein the composition interferes with the interaction of an apelin polypeptide or apelin peptide with APJ.

4. The method of claim 1, wherein the composition comprises an anti-lymphangiogenesis agent that inhibits a factor selected from the group consisting of VEGF-C, VEGF-D, and VEGFR3.

5. The method of claim 1, wherein the composition comprises an anti-apelin antibody or fragment thereof.

6. The method of claim 5, wherein the antibody or fragment thereof binds a polypeptide that is selected from the group consisting of: a. a polypeptide as defined in SEQ ID NO:1; b. a polypeptide as defined in SEQ ID NO:2; c. a polypeptide as defined in SEQ ID NO:3; d. a polypeptide as defined in SEQ ID NO:4; e. a polypeptide as defined in SEQ ID NO:5; and f. a polypeptide having at least 80% sequence identity with the polypeptide of a) through e) above.

7. The method of claim 5, wherein the antibody or fragment thereof binds the polypeptide of SEQ ID NO:4.

8. The method of claim 5, wherein the antibody or fragment thereof binds a polypeptide that has at least 90% sequence identity with the polypeptide or peptide of SEQ ID NO:1, SEQ H) NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5; and that interacts with APJ.

9. The method of claim 1, wherein the inhibitor of apelin activity is an anti-APJ antibody or fragment thereof.

10. The method of claim 1, wherein the inhibitor of apelin activity is selected from the group consisting of: a. an apelin antisense nucleic acid, receptor decoy, ribozyme, sense polynucleotide, double stranded RNA, RNAi, aptamer, and small molecule antagonist; and b. an APJ antisense nucleic acid, receptor decoy, ribozyme, sense polynucleotide, double stranded RNA, RNAi, aptamer, and small molecule antagonist.

11. The method of claim 1, wherein the inhibitor of apelin activity is an inhibitor of a serine protease that cleaves a polypeptide specifically after an arginine residue.

12. The method of claim 1, wherein the composition comprises a pharmaceutically acceptable carrier.

13. The method of claim 1, wherein the biological sample is from a mammal.

14. The method of claim 1, wherein the biological sample is a human biological sample.

15. The method of claim 14, wherein the biological sample is in a patient and wherein the patient has a disease or condition involving lymphangiogenesis.

16. The method of claim 15, wherein the composition is introduced by a route selected from the group consisting of subcutaneous injection, intravenous injection, intraocular injection, intradermal injection, intramuscular injection, intraperitoneal injection, intratracheal administration, epidural administration, inhalation, intranasal administration, oral administration, sublingual administration, buccal administration, rectal administration, vaginal administration, and topical administration.

19. The method of claim 15, further comprising c. administering to the patient a therapeutically effective amount of an anti-cancer agent, wherein the anti-cancer agent is selected from the group consisting of a chemotherapeutic agent, a radiotherapeutic agent, an anti-angiogenesis agent, an anti-lymphangiogenesis agent, and an apoptosis-inducing agent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Primary Examiner, Art Unit 1643